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Full Length Research

Biochemical Indices of Combined Measure of Serum Uric Acid and Beta Human Chorionic Gonadotropin (β hCG) Versus Serum Uric Acid alone as Prognostic Indicators of Pregnancy Outcome of Preeclampsia

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Possible biochemical indices of preeclampsia have been sought for many years. The aim of this study is to evaluate the accuracy of combined measure of maternal serum uric acid level and quantitative serum beta hCG versus serum uric acid level alone as prognostic indicators of pregnancy outcome among preeclamptic patients at the Federal Medical Centre, Yenagoa. This is a hospital based prospective case control study by systematic sampling selection. The two groups comprised of 100 consecutive patients each, one with pre-eclampsia (study group) and the other without pre-eclampsia (control) admitted for management into the antenatal ward and labour ward over the seven-month period of the study. The values of their serum uric acid and beta hCG levels were evaluated on admission and followed up. Data entry and statistical analysis were done using statistical package for social science (windows version 22.0. SPSS Inc; Chicago, USA). Level of significance was set at P < 0.05. The mean serum uric acid level was higher amongst participants with preeclampsia (405.6 ± 99.5 µmol/L) than in those without preeclampsia (232.7 ± 26.3 µmol/L) and this difference was statistically significant (p= 0.001). The prognostic accuracy in predicting pregnancy outcomes were: HELLP syndrome (0.25, 0.44), Eclampsia (0.13, 0.50), Acute Renal Failure (0.27, 0.44), IUGR (0.31, 0.43), IUFD (0.27, 0.38) and Birth Asphyxia (0.35, 0.49) respectively for serum uric acid alone and combined measure of serum uric acid and serum β hCG. Serum uric acid levels were found to be useful prognostic indicators for feto-maternal outcome in women with preeclampsia. However, combined measure of serum uric acid and serum β hCG level in prognosticating pregnancy outcome in preeclamptic women was shown to have a better accuracy than either serum uric acid.

Key words: Preeclampsia, pregnancy outcome, prognostic indicators and accuracy, uric acid.

INTRODUCTION

Possible biochemical indices of preeclampsia have been sought for many years (Sazina et al., 2008). Some of these include serum uric acid assay, serum beta human chorionic gonadotropin, serum fibronectin, as well as serum calcium and trace elements. Principally, it is now agreed that hyperuricaemia is a feature of preeclampsia (Sazina et al., 2008). Serum uric acid is also a reliable index of fetal wellbeing when pregnancy is complicated by preeclampsia. With hyperuricaemia, prognosis for the fetus is poor irrespective of level of blood pressure. It identifies women with increased risk of adverse maternal and particularly fetal outcome (Rajalaxmi et al., 2014).

A number of placental peptides have been associated with the severity of preeclampsia and these include beta human chorionic gonadotropin (β hCG). Preeclampsia is characterized by disturbed trophoblastic physiology hence early placental dysfunction could be reflected by altered hCG concentration (Na, 2009). The relationship between increasing β hCG levels and severity of preeclampsia was first noted by Smith and Smith (1934). Since then numerous studies have suggested that elevated maternal serum β hCG level may be associated with severe preeclampsia. A recent study by Kalkunte et al., (2010), found higher hCG levels in serum from preeclamptic pregnancies at term compared with serum derived from normal pregnancies. Altered glycosylation patterns and/or presence of Sialyl Lewis antigens on hCG have been associated with the pathogenesis of preeclampsia, which weakens the enrolment and/or development of tolerance – inducing immune cell types (Chinedu et al., 2017). Vandana et al., (2016), found a strict relationship between severe preeclampsia and elevated serum beta hCG levels. Their findings also suggested that severe preeclamptic women have higher hormonal changes than mild preeclamptic women and reflects the abnormal placentation in these patients. The first report of increased maternal serum uric acid concentration in preeclampsia/eclampsia was published in 1917 (Slemons and Bogert, 1917). Subsequently, Lancet and Fisher (1956), were among the first to note a positive association between uric acid levels and the severity of preeclampsia. A similar study by Roger (1990) in Australia supported strongly the work of Ben Bridge and Roberts as it concluded that rise in serum uric acid in patients with preeclampsia is secondary to placenta damage rather than alteration in renal function. A work done in Nigeria by Wakwe and Abudu (1999) in which 59 women attending antenatal clinic had their plasma uric acid and creatinine clearance measured confirmed that serum uric acid was able to differentiate between normal pregnancy and pregnancy induced hypertension at $p < 0.002$. A further rise in serum uric acid in patients with preeclampsia can also predict eclampsia (Azza, 2010). Bakheit (2002) in his research in Sudan found that the increasing level of serum uric acid correlates well with the severity of hypertension in a study by Redman and Beil (1976) in South Africa, analysed plasma urate and blood pressure in 332 pregnant women with hypertension. Perinatal mortality was markedly increased when maternal plasma uric acid was raised. They found that maternal hypertension even severe without hyperuricaemia was associated with an excellent prognosis for the fetus. They concluded that in terms of fetal death, serum uric acid may be more important than blood pressure (Azza, 2010). Preeclampsia is a common problem globally particularly in developing countries with very minute resources (Agboola, 2006; Adeosun et al., 2015; Ekine et al., 2015; Kwakume and Ekele, 2015). Federal Medical Centre, Yenagoa is at the crux of this challenge. This study therefore aimed to determine and compare serum uric acid alone versus combined serum uric acid and quantitative serum beta human chorionic gonadotropin among preeclamptic patients and non-preeclamptic patients and to determine pregnancy outcomes associated with them, so as to act as prognostic indicators that would guide our future management of preeclampsia.

MATERIALS AND METHODS

The study was conducted in the Obstetrics and Gynaecology Department of the Federal Medical Centre, Yenagoa, Bayelsa State. The hospital is a tertiary health institution that provides all levels of health care services to patients especially in Bayelsa, Rivers and Delta states. It was a prospective case control study by systematic

sampling selection. The first group of the study population comprised 100 consecutive Preeclamptic patients admitted for management into the antenatal ward and labour ward of Federal Medical Centre, Yenagoa over the period of the study. The second group (control) of the study population comprised 100 consecutive non-preeclamptic patients admitted for management into the antenatal ward and labour ward. The values of their serum uric acid were evaluated on admission. Patients were followed up to delivery and their pregnancy outcome evaluated. The study was carried out from the 1st of April 2018 to the 30 of September 2018.

Ethical Approval

Written and informed consent were obtained from every participant in this study. The hospital research and ethics committee examined and approved this research work. Inclusion criteria constituted all preeclampsia patients admitted into the antenatal ward and labour ward of Federal Medical Centre, Yenagoa, who consented to be part of the study within the study period and the controls were normal healthy pregnant women whose serum uric acid levels were assessed within the same period. Exclusion criteria included patients with chronic hypertension, chronic hypertension with superimposed preeclampsia, pregnancy induced hypertension, renal disease, diabetes mellitus, heart failure and ischemic heart disease. Women who refuse to give consent were also excluded from the study.

Sample size: The sample size for the study was calculated using the formula:

$n= z^2pq/d^2$ (Felix et al., 2016)

n = minimum sample size

z = standard normal deviation set at 95% confidence limit = 1.96

p = prevalence of preeclampsia in previous study

q =1-p (complementary probability)

d = margin of error = 5% = 0.05

Prevalence of preeclampsia that was used in this study based on a previous study done in Bayelsa state was 5.6% (Ekine et al., 2015). Therefore, giving an attrition of 10%, the minimum sample size was 89. However, this was adjusted to 100 for ease. Thus, 100 patients who met the inclusion criteria were recruited for this study. In our centre, about 400 patients register for antenatal care per month and about 5%-10% when followed up to the third trimester are estimated to develop preeclampsia. This study was carried out within 5 months.

Method

Patients were recruited consecutively as they were admitted into the antenatal ward and labour ward with preeclampsia. Thorough history and examination were used in selecting patients based on the inclusion and exclusion criteria. The blood pressure was measured with the use of manual sphygmomanometer while the patient was in supine position on a couch with a left side tilt. An appropriate size cuff that covers at least 2/3rd of the upper arm was used. The systolic blood pressure was taken at the first point the sound was heard while the diastolic blood pressure was taken as Korotkoff V.A patient was said to be hypertensive when her blood pressure was persistently equal to or greater than 140/90 mmHg measured at least 6 hours apart.

Specimen Collection

Urine collection was done in the antenatal ward and labour ward. Patients were trained and instructed adequately on how to collect clean catch midstream urine. This involved initial cleaning of the vulva with copious amount of clean water. The labia were parted, and the first part of the urine was voided and the next stream of urine (about 5 millilitre) was collected into a clean, dry urine bottle with patient's name and number written on it. Trained nurses were recruited to supervise the process. The urine specimen was taken to the laboratory for protein estimation and in suspicious cases, urine microscopy, culture and sensitivity was done to exclude urinary tract infection (UTI). Protein estimation was based on the colour changes of the dipstick compared to the corresponding colour chart on the reagent container. The diagnosis of proteinuria was made when two midstream samples of urine collected at least four hours apart showed one or more plus of albumin using dipstick (Sreelatha et al., 2015). For the diagnosis and classification of preeclampsia, Davey and McGillivray's classification adopted by the International Society for the Study of Hypertension in pregnancy (ISSH) was used. Patients that met the criteria for preeclampsia were recruited into the study. Once the diagnosis was confirmed, blood specimen was collected from the patient for uric acid analysis. Urine specimen and blood specimen were

also collected from normal non preeclamptic (healthy pregnant women) as controls. About Five millilitres of blood was collected via aseptic procedure into a plane specimen bottle. Serum was separated by centrifugation for ten minutes at 3500 revolutions per minute (rpm). The supernatant was transferred by Pasteur pipette into a test tube for immediate analysis or stored at 2-8^{0}C until time of analysis usually within 24 hours. Analysis of uric acid was done by Phosphotungstic acid method (Lincy et al., 2016) and the results were read by spectrophotometer.

Data Collection

Socio-demographic data and clinical characteristics such as age, tribe, marital and booking status was obtained and recorded in the protocol. In addition, the gestational age at delivery, birth weight, 5-minute Apgar scores and admission to special care baby unit was noted. Adverse perinatal outcomes like intrauterine growth restriction (IUGR), Birth Asphyxia and Intrauterine fetal death (IUFD) were also noted. Mothers admitted into intensive care unit were followed up and their outcomes recorded. Maternal adverse outcomes such as Eclampsia, Acute renal failure and HELLP syndrome were also noted. Laboratory results for uric acid and proteinuria were also collected.

Data Analysis

Data entry and statistical analysis were done using statistical package for social science (IBM SPSS for windows version 22.0. SPSS Inc; Chicago, USA). Percentages, means and standard deviations were calculated. Chi-square was used to determine association between qualitative variables. Student t-test was used to determine association between quantitative variables. Level of significance was set at $P < 0.05$. Tables were used to illustrate patterns of variables. Sensitivity, specificity, predictive values and accuracy were calculated for the serum markers in relation to fetal and maternal outcomes of women who had preeclampsia.

RESULTS

A total of 200 participants were involved in this study which constituted One hundred preeclamptic women (study group) and one hundred non preeclamptic women (control group) with a 100% response rate. The predominant age group in both the study group and the control group was 25 - 34 years age group with 52 (52.0%) and 56 (56.0%) respectively. The mean age in the study group was 28 ± 6.7 years, while in the control it was 31 ± 6.5 years. The difference in age between the groups was not statistically significant ($p = 0.53$). Majority of the patients were of the Ijaw ethnic group both in the preeclamptic and control groups with 62 (62.0%) and 56 (56.0%) respectively. Most of the patients were married in both the preeclamptic and control groups with 84 (84.0%) and 92 (92.0%) married respectively. Amongst those that were married, most of the marriages were in the monogamous setting; 78 (92.9%) in the preeclamptic and 89 (97.7%) in the control group. Most of the patients were Christians in both the preeclamptic and control groups with 94 (94.0%) and 96 (96.0%) respectively. The highest level of education was secondary school in the preeclampsia group (58%), while it was tertiary education for controls (54%). Majority 56 (56%) and 54 (54%) of the participants in both the preeclamptic and control groups respectively were businesswomen by occupation.

There was no statistically significant ($p =0.09$) association between the combined markers and the occurrence of eclampsia. Amongst those with elevated markers, 21.56% (11/51) had eclampsia. There was no statistically significant ($p =0.45$) association between the combined markers and the occurrence of acute renal failure. Amongst those with elevated markers, 7.84% (4/51) had acute renal failure. There was also no statistically significant ($p =0.15$) association between the combined markers and the occurrence of HELLP syndrome. Amongst those with elevated markers, 5.88% (3/51) had HELPP syndrome. There was a statistically significant ($p = 0.007$) association between the combined markers and the occurrence of severe hypertension. Amongst those with elevated markers, 96.07% (49/51) had severe hypertension. There was no statistically significant ($p = 0.44$) association between the combined markers and the occurrence of IUGR. Amongst those with elevated markers, 15.68% (8/51) had IUGR. There was no statistically significant ($p =0.65$) association between the combined markers and the occurrence of IUFD. Amongst those with elevated markers, 3.92% (2/51) had IUFD. There was no statistically significant ($p = 0.13$) association between the combined markers and the occurrence of birth asphyxia. Amongst

Table 1. Relationship between biochemical risk factors and maternal/fetal complications in preeclamptic participants.

RISK	COMPLICATIONS						
HIGH URIC ACID LEVEL n=69	HELLP n (%)	ECLAMPSIA n (%)	ARF n (%)	IUGR n (%)	IUFD n (%)	BIRTH ASPHYXIA n (%)	SEVERE HTN n (%)
PRESENT	3 (4.34)	13 (18.8)	5(7.24)	9 (13)	6 (8.7)	15 (21.8)	61(88.4)
ABSENT	66 (95.7)	56 (81.2)	64 (92.76)	60 (87)	63 (91.3)	54 (78.2)	8(11.6)
P VALUE	P=0.46	P=0.03*	P=0.27	P=0.13	P=0.07	P=0.001*	P=0.03*
COMBINED MARKER HIGH LEVEL n=51	HELLP n (%)	ECLAMPSIA n (%)	ARF n(%)	IUGR n (%)	IUFD n (%)	BIRTH ASPHYXIA n (%)	SEVERE HTN n (%)
PRESENT	3 (5.88)	11(21.6)	4(7.84)	8(15.7)	2(3.92)	17(33.3)	49(96.8)
ABSENT	48(94.12)	40(78.4)	47(92.16)	43(84.3)	49(96.08)	34(66.7)	2(3.2)
P VALUE	P=O.15	P=0.09	P=0.45	P=0.44	P=0.65	P=0.13	P=0.007*

Key: * statistically significant P-value.

Table 2. Prognostic accuracy scoring of the different serum markers.

Pregnancy outcome/ Serum marker	Sensitivity	Specificity	PPV	NPV	Accuracy
Severe HTN					
Uric acid	85	50	87.1	45.45	0.78
Combined	71.25	90	96.61	43.90	0.75
HELLP					
Uric acid	100	22.68	3.84	100	0.25
Combined	100	42.27	6.81	100	0.44
ECLAMPSIA					
Uric acid	100	25.29	16.67	100	0.13
Combined	84.62	44.82	18.64	95.12	0.50
ACUTE RENAL FAILURE					
Uric acid	100	23.15	6.41	100	0.27
Combined	80	42.11	6.78	97.56	0.44
IUGR					
Uric acid	90.91	23.59	12.82	95.45	0.31
Combined	90.91	44.94	20.00	97.56	0.50
IUFD					
Uric acid	85.71	22.58	22.22	95.65	0.27
Combined	28.57	38.71	5.30	87.80	0.38
BIRTH ASPHYXIA					
Uric acid	80.95	24	22.97	81.81	0.35
Combined	76.19	44	27.59	86.84	0.49

those with elevated markers, 33.33% (17/51) had birth asphyxia. Table 1 shows the relationship between biochemical risk factors and maternal/fetal complications. Table 2 shows sensitivity, specificity,

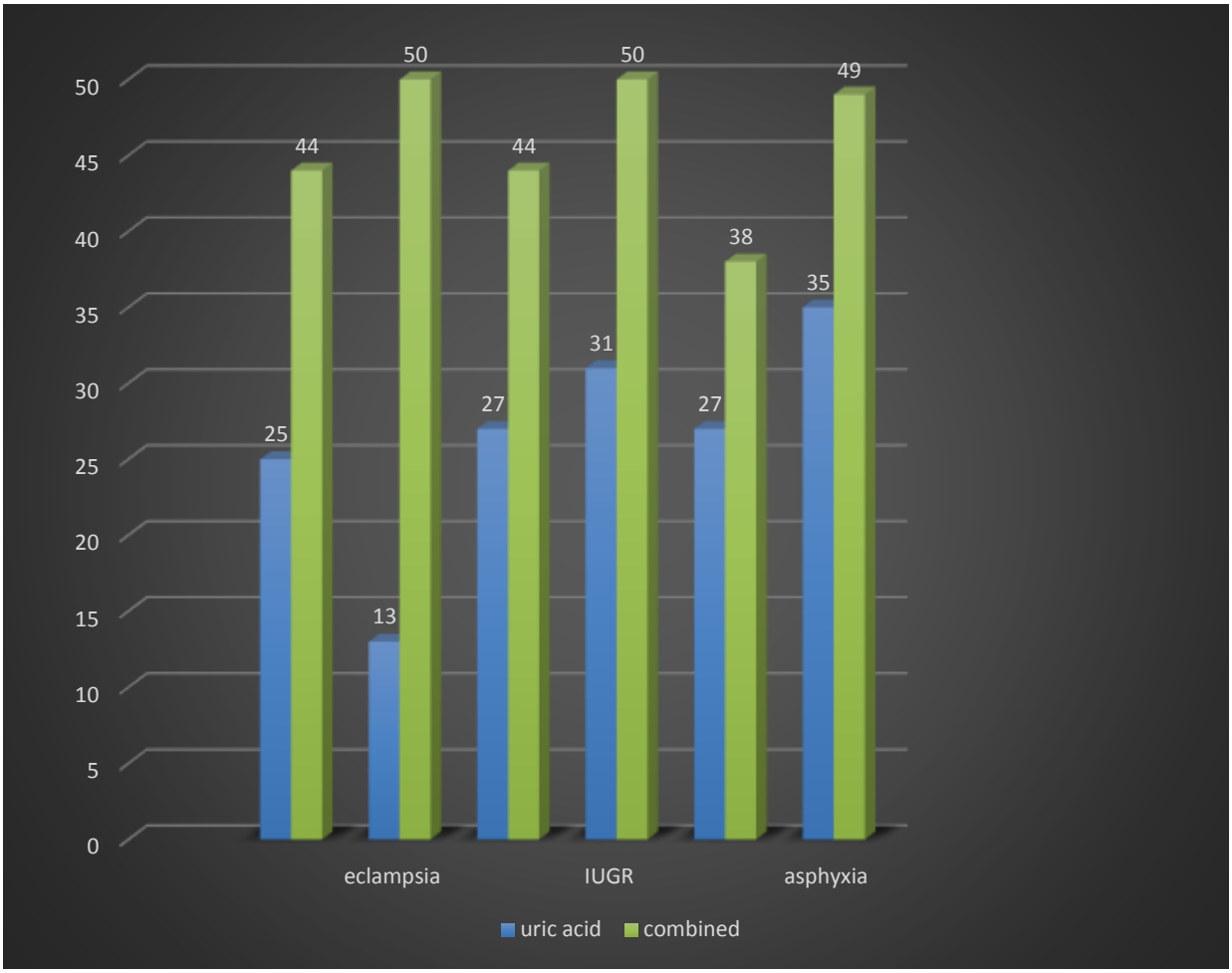

Figure 1. Bar chart showing the accuracy of serum markers in predicting adverse pregnancy outcome.

predictive values and accuracy for the serum markers in relation to fetal and maternal outcomes of women who had preeclampsia. Figure 1 shows the accuracy of serum markers in predicting adverse pregnancy in preeclamptic patients.

DISCUSSION

In this study, the mean age of cases and controls were 28 ± 6.7 and 31± 6.5 respectively. The mean age of cases is higher than 27± 4.9 and 27.2± 5.6 years reported in Calabar and Ogun respectively (Kooffrey et al., 2014; Sotunsa et al., 2016). The results from this study are consistent with the usual risk factors for preeclampsia including primipaternity and family history of preeclampsia. Primipaternity was more common in the study group (70%) than in the control group (45%) with the difference being statistically significant (p = 0.00). This is in keeping with theories surrounding the origins of preeclampsia identifying pregnancy by a new spouse or partner as a risk factor for the condition (Agboola, 2006).

More women in the study group (35%) as compared to the control group (7%) had a family history of hypertensive disease in pregnancy. Genetic factors have been implicated in the development of preeclampsia. Daughters of women with preeclampsia are about four times more likely to develop the disease than daughter in-laws and it has been established that it is familial (Agboola, 2006; Yakassai and Morhason-Bello 2013).

The mean serum uric acid level was higher

amongst participants with preeclampsia (405.6 ± 99.5 µmol/L) than in those without preeclampsia (232.7 ± 26.3 µmol/L) and this difference was statistically significant (p= 0.001). This increased amount of serum uric acid amongst clients with preeclampsia has been reported by several studies and this increased amount is thought to correlate with the severity of the disease condition (Sazina et al., 2008; Azza, 2010; Prathap and Kondareddy, 2016; Asgharnia et al., 2017). Antenatal patients with renal disease were excluded from taking part in this study and as such, it is unlikely that renal disease would have contributed to the higher levels of serum uric acid amongst the study population. For the maternal outcomes, there was a statistically significant association between serum uric acid levels and eclampsia (p = 0.00) as well as acute renal failure (p = 0.01). The association between serum uric acid and HELLP syndrome was not statistically significant (p = 0.06). There was a statistically significant association between serum uric acid and IUGR (p = 0.00), IUFD (p = 0.02) and birth asphyxia (p = 0.00). There have been conflicting reports (Lancet and Fisher, 1956; VAjZquez-RodrAquez and Rico-Trejo, 2011; Paternoster et al., 1999; Martin and Brown, 2010) on the ability of serum uric acid to predict adverse pregnancy outcomes. The wide variation in gestational ages may have accounted for the different opinions found in these studies. In this study, majority (94%) of the patients recruited into the study group were at least 34 weeks gestational age and irrespective of the preeclamptic status of the patient, the serum uric acid levels are bound to rise as pregnancy approaches term (Razia and Nasima, 2013).

The ability of the combined markers to predict an adverse pregnancy outcome was measured against the ability of the individual markers on their own. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each of the markers was calculated and then also calculated for the combined marker. The prognostic accuracy in predicting pregnancy outcomes were: HELLP syndrome (0.25, 0.44), Eclampsia (0.13, 0.50), Acute Renal Failure (0.27, 0.44), IUGR (0.31, 0.43), IUFD (0.27, 0.38) and Birth Asphyxia (0.35, 0.49) respectively for serum uric acid alone and combined measure of serum uric acid and serum β hCG. The combined measure showed a better accuracy in predicting the maternal and fetal outcome than either serum uric acid or serum β hCG. While there are a number of biochemical tests that have been used to predict the occurrence or severity of preeclampsia, evidence by Razia and Nasima (2013); suggests that a combination of the markers leads to improved predictability as was seen in this study.

The study involved a single estimation of serum uric acid and quantitative serum β hCG. It would have been enriched if several samples were taken to monitor any diurnal variation and document possible disease progression, recommended for future studies.

CONCLUSION

Serum uric acid levels were found to be useful prognostic indicators for feto-maternal outcome in women with preeclampsia. However combined measure of serum uric acid and serum β hCG level in prognosticating pregnancy outcome in preeclamptic women was shown to have a better accuracy than either serum uric acid.

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